FRIBERG, L., Karolinska Institute, Stockholm, Sweden

"Smoking and health." (Letter: Lancet II: 973, November 4, 1972)

"Dr. Cherry and Professor Forbes are sceptical of Professor Burch's proposal of worldwide twin studies. One reason given is that, at present, there is little evidence that such studies would alter the main conclusions concerning the effects of cigarette smoking on health. For certain pulmonary diseases (e.g., lung cancer) the causal relationship with cigarette smoking is quite clear. On the other hand, twin studies might well be of substantial value even for these effects -- for example, to find out whether certain persons are more susceptible than others to an effect of cigarette smoking. For other effects, including high mortality in general and particularly, for example, in coronary heart-disease, we feel that the case against cigarette smoking per se is not all that strong and in our opinion international collaboration using twins as target populations would be extremely useful. The problem in twin studies, even using a population the size of Sweden's, is to get enough numbers in different, well-defined smoking discordant groups. We are happy to learn that Dr. Cherry and Professor Forbes do not live up to their own objections to creating new registries. As can be seen in a recent paper of theirs, they state, 'A twin study is being planned, partly to investigate further the observations, on smoking discordant twins, reported by Friberg et al....'

"While large-scale twin studies until now have primarily focused on the health consequences of smoking, the twin method has a much broader applicability to a large number of medical and social problems concerned with the interrelationships between environmental agents and their impact upon the genetic constitution. The importance of these interrelationships was precisely the reason for a recent expansion of the Swedish twin registry in collaboration with the National Environment Protection Board to include an additional 15,000 pairs born from 1926 to 1942."

8. CANCER IMMUNOLOGY

RUCKDESCHEL, J.C., CODISH, S.D., STRANAHAN, A. & McKNEALLY, M.F., Albany Medical Center, New York

"Postoperative empyema improves survival in lung cancer. Documentation and analysis of a natural experiment." (The New England Journal of Medicine 287/20: 1013-17, November 16, 1972)

"A retrospective chart study revealed improved survival rates in patients in whom empyema developed after surgical resection for carcinoma of the lung. The overall five-year survival rate for the empyema group of 18 patients was 50 per cent, compared to an 18 per cent five-year survival rate in a control group consisting of a random 34-patient sample of resected cases at this institution. On further analysis, the beneficial effect of intrapleural infection was found principally in patients with tumor limited to the lung and its draining regional lymph nodes. Six of seven patients in this group survived for five years.

002367047

Source: https://www.industrydocuments.ucsf.edu/docs/ptxk0000

"The protection from recurrent cancer conferred on these patients by postoperative empyema may have been mediated by the activation of regional cellular immune mechanisms. The reaction between immune lymphocytes and bacterial antigens is believed to release lymphokines and activate macrophages that nonspecifically destroy residual tumor cells while containing the intrapleural infection."

MOORE, G.E., Roswell Park Research Institute, Buffalo

"Iatrogenic immunotherapy of lung cancer." (Editorial: The New England Journal of Medicine 287/20: 1042-3, November 16, 1972)

"The study reported in this issue is interesting and supports similar reports but suffers from the inconsistencies that plague most retrospective clinical studies. Perhaps the surviving patients with empyema represent a select group; those with residual cancerous tissue may have been more susceptible to the infection and died within 30 days. No mention is made of empyema after the 30-day period; it is difficult to believe that it did not occur. A number of authors have reported approximately the same five-year survival in patients treated by lobectomy or pneumonectomy. It is strange, therefore, that in this study all the patients in the 'cured' empyema group had had pneumonectomies, whereas in the control patients, there were an equal number of long-term survivors after both procedures....

"But the heart (and lungs) of the matter is the nature of carcinolysis if it occurs. The authors have depreciated the role of a direct effect of the bacteria on tumor cells and have suggested that an immunologic reaction is most likely....

"Model experiments to test the thesis presented in this report would be difficult, but not impossible to design. Squamous carcinomas of the bronchi can be induced in rodents, and one could easily collect a mixed bag of organisms from most operating rooms. The use of a parallel experiment with germ-free animals should help to separate the effects of bacterial infection from those of immune reactions.

"It is humiliating that we have not been able to eliminate the health hazards of cigarette smoking and thus reverse the pandemic of lung cancer. Successful preventive measures would eliminate the desperate consideration of empyema as a curative adjunct to lung-cancer surgery."

PFEIFFER, E.H., Mainz University, West Germany

"Untersuchungen uber die Wirkung der Pockenvakzination auf die Entstehumg 3,4-Benzpyren-induzierter Tumoren." (Studies on the effect of small pox vaccination upon the development of 3,4-Benzo(a)pyrene-induced tumors) (Zentralblatt fur Bakteriologie, Parasitenkunde, Infektionskrankheiten und Hygiene 156/1: 115-128, 1972: author's English abstract)

00236048

"The objective of our experiments with male NMRI mices was, to determine the influence of the small pox vaccination on the development and the periods of development of the 3,4-Benzo(a)pyrene-induced tumors as well as the time of survival of the tumor bearing animals. After a s.c. injection of 10 mg Benzo(a)pyrene which was suspended in polyethylene glycol

Source: https://www.industrydocuments.ucsf.edu/docs/ptxk0000

diluted with physiological NaCl-solution an immunization with vaccinia virus was performed 8 days later.

1. Compared with the control group which had Bp applied only, the time progress of development of the tumor was different. A statistical analysis of the tumor rates per period during the experiment resulted in significant difference after the ending period of 10th, 12th and 14th week.

2. The average latent period of development of the tumor was reduced significantly by a one-time small pox vaccination.

3. A statistical analysis of the death rates which was made on the basis of the life table method in analyzing survival revealed a significant difference in the interval of the 16th and the 18th week.

4. A statistically significant difference could not be calculated at the average life time.

5. An effect on the total tumor rates could not be determined because of the very high doses of Benzo(a)pyrene application.

6. A two-time small pox vaccination revealed the same results as the one-time vaccination."

HANNA, M.G., Jr., TENNANT, R.W., YUHAS, J.M., CLAPP, N.K., BATZING, B.L. & SNODGRASS, M.J., Oak Ridge National Laboratory, Tennessee

"Autogenous immunity to endogenous RNA tumor virus antigens in mice with a low natural incidence of lymphoma." (Cancer Research 32: 2226-34, October 1972)

"The immune reactivity to endogenous (wild-type) RNA tumor virus-related antigen(s) was evaluated in RF mice, a strain with a low natural incidence of lymphoma. The purposes were to determine whether maintained humoral immunity could be detected and to evaluate the response with respect to the immune-mediated pathogenesis of glomerulo-sclerosis and incidence of tumors of lymphatic origin. Measurements of detectable murine leukemia virus antigen in the thymus and spleen were correlated with the development of immune competence, glomerulosclerosis, and the incidence of lymphoid neoplasia. Also, the specificity of the antibody that lodged in the kidney was determined by elution and indirect immunofluorescence with Gross virus-infected cells. A marked decrease in detectable murine leukemia virus antigen in thymus and spleen was found to correlate with development of immunological competence of the spleen as assayed by de novo germinal-center formation, antigen localization, and immune elimination from serum, which in turn correlated with occurrence of glomerulosclerosis. The antibody in the kidney was determined to be specific for Gross virus antigen(s). The role of this autogenous immunity may be considered to be beneficial in the RF mouse, as data correlating natural lymphoid neoplasia with severity of immune-complex glomerulosclerosis indicates that an inverse relationship is established in aged animals."

0002367049

Source: https://www.industrydocuments.ucsf.edu/docs/ptxk0000

TAN, E.M. & LERNER, R.A., Scripps Clinic and Research Foundation, La Jolla, California (CTR-grant)

"An immunological study of the fates of nuclear and nucleolar macromolecules during the cell cycle." (Journal of Molecular Biology 68: 107-14, 1972)

"Immunofluorescence employing specific antibodies was used to detect nuclear and nucleolar macromolecules during the cell cycle in synchronized diploid human lymphocytes. The majority of 'available' native DNA determinants were adjacent to the nuclear membrane in phase G_1. DNA associated with histones was present throughout the nucleus in phases G_1 and S and associated with chromosomes in metaphase. Single-stranded DNA was not detected in phase G_1 cells, but midway through phase S it was abundantly present. The morphology of the nucleolus changed markedly as cells proceeded from G_1 to metaphase, and in metaphase nucleolar fragmentation and the appearance of nucleolar contents in the cytoplasm were observed. Cytoplasmic DNA, which was not seen in G_1 or S-period cells, appeared adjacent to plasma membranes in metaphase cells.

"These studies demonstrated that specific antibodies against nuclear and nucleolar macromolecules could be important reagents for determination of the fates of certain macromolecules in eukaryotic cells."

9. PSYCHOLOGY

ABSE, D.W., WILKINS, M.M., KIRSCHNER, G., WESTON, D.L., BROWN, R.S. & BUXTON, W.D., University of Virginia Hospital, Charlottesville

"Self-frustration, nighttime smoking and lung cancer." (Psychosomatic Medicine 34/5: 395-404, September-October 1972)

"Two studies are described in which 65 lung disease patients were studied. Thirty-six of these patients had lung cancer; 29 had chest diseases other than lung cancer. Among the interview questions concerned with smoking behavior, the question of nighttime smoking aroused the greatest hesitation among patients. Sensitivity to this issue was found to be particularly great among lung cancer patients interviewed by a physician who did not smoke. In spite of this influence, however, cancer patients as a group did report more frequent nighttime smoking. It was also found that, while cancer patients had been smoking for a longer period of time and were smoking a greater amount, their nighttime smoking habits were not related to either of these variables. And finally, the observation that younger cancer patients smoke more frequently at night than do older cancer patients, suggested that the age of (cancer) onset may be significantly influenced by nighttime smoking habits.

0002367050

"We note that the smoking habits of lung cancer patients seem to occur within a very different psychophysiologic context than do the smoking habits of the general public. We are led to the conclusion, suggested by Eastwood and Trevelyan, that a classification of smoking patterns would be extremely useful. For example, it would be interesting to study cancerous and noncancerous smokers in terms of Russell's typology of smoking behaviors. On the basis of the present findings, we would expect lung cancer patients to evidence less psychosocial and indulgent smoking and perhaps more

Source: https://www.industrydocuments.ucsf.edu/docs/ptxk0000

tranquilization and addictive smoking. If so, such a finding would help us understand in what way the cancer patient's smoking habits differ and how these differences relate to his psychologic makeup....

"Given a possible link between nighttime smoking and increased susceptibility to lung cancer, it is necessary to understand why lung cancer patients so often smoke at night. The personality of the lung cancer patient, as depicted in the present study and in the general literature, suggests that these patients evidence a great deal of anxiety or depression, unrelieved through normal or neurotic channels of discharge. In fact, they score significantly lower on measures of neuroticism: they strive for independent self-expression and an avoidance of emotional and social involvements: and finally, they tend to report fewer psychosomatic complaints and greater stability in their marital lives.

"It is very interesting to compare these descriptions with those of smokers in general. Here, we find that smokers are a) impulsive, danger seeking and emotionally labile; b) more extroverted and more prone to psychosomatic disorders; and c) more often in the divorced or widowed category and more neurotic.

"These two descriptions, diametrically opposed, suggest that the psychologic characteristics associated with cigarette smoking clearly distinguish the lung cancer patient from the cancer-free smoker. Such characteristics, occurring within the context of progressively impaired emotional gratification, may contribute to the cancer patient's reported sleeplessness and tendency to smoke at night. Nighttime smoking, particularly during the later part of middle-age, may indicate an incipient though uncomplaining form of neurotic decompensation for several years prior to emergence of lung cancer symptoms....

"A further study, now being completed by the authors, contrasts cancer patients who smoke at night with a matched control group who also smoke at night. The former group is distinguished by evidence of poor interpersonal communication, inadequate sexual adjustment and conflicts involving both dependency and aggression. Thus it seems that for the cancer patient nighttime smoking is associated with a general impairment in emotional gratifications."

COBB, S., University of Michigan, Ann Arbor
versus
ABSE, D.W., WILKINS, M.M., BUXTON, W.D., BROWN, R.S., KIRSCHNER, G. & WESTON, D.L., University of Virginia

"Nighttime smoking and lung cancer." (Psychosomatic Medicine 34/5: 385-7, September-October 1972)

COBB:

"In this issue there is a paper by Abse and co-workers entitled Self-Frustration, Nighttime Smoking and Lung Cancer. This paper contains a curious interaction between astute clinical observation and an insensitivity to the meaning of numerical data. First, the authors are to be congratulated for presenting their data in sufficient detail to permit reanalysis....

2023677051

Source: https://www.industrydocuments.ucsf.edu/docs/ptxk0000

"The authors started with an hypothesis based on preexisting, well-supported clinical evidence that self-frustration of the need for stimulation is associated with lung cancer. They then postulate that nighttime smoking is the intervening variable. The hypothesis then goes as follows: self-frustration leads to nighttime smoking, and nighttime smoking increases the risk of lung cancer. In order to test the second part of this hypothesis, they have collected smoking histories on hospitalized patients with lung cancer and other lung diseases.

"When they started looking at their numbers, they found a significant bias in the data. It appears that those interviewed by smokers or interviewed in depth reported more nighttime smoking than those interviewed by nonsmokers. This they interpret as a response bias. However, improbable samples do arise by chance, and it is possible that by chance or by some vagary of the selection process the samples are simply different. If one assumes response bias, it is improper to combine samples. If one assumes sampling variation, one should combine the samples....

"At this point it is reasonable to conclude that the second part of the authors' hypothesis, that nighttime smoking is associated with increased risk of lung cancer, is supported for those who have smoked for less than 35 years. The sample is inadequate for concluding that such an effect does not occur among those who have smoked for 35 years or more; however, no evidence for a positive association was found in this long-smoking group. Perhaps nighttime smoking just does not add much to the risk of lung cancer for those who have already smoked so long.

"The authors started with evidence for the association of self-frustration with lung cancer. They have demonstrated an association of nighttime smoking and lung cancer. Then they adduced evidence from an as yet incomplete study that this self-frustration is associated with lung cancer independent of nighttime smoking. This is the only reasonable conclusion from a study of nighttime smokers with and without lung cancer that shows an association of self-frustration with lung cancer. We are now left with the probable conclusion that nighttime smoking and self-frustration may separately contribute to lung cancer.

"The authors are to be congratulated for having made an important contribution to our understanding of the relationship of smoking to lung cancer. It is to be hoped that they will further pursue the issue of self-frustration and lung cancer and further investigate the attractive, but so far unsupported, hypothesis that self-frustration contributes to lung cancer via nighttime smoking. Finally, an actual test of the hypothesis that cancer patients, but not other patients, are more willing to report their nighttime smoking to smokers rather than to nonsmokers, might lead to a further understanding of the problems of bias in self-report."

2002367052

ABSE et al:

"The approach which Cobb recommends, appears contrary to some basic principles of hypothesis testing. Without prior statistical justification, Cobb recombined our samples in a very selective fashion. His basis for selection -- ie, whether or not the patient had been smoking for 35 years, resulted in the exclusion of 74% of the cancer patients but only 11% of their controls. Such a drastic alteration of the original sample seriously affects the interpretation of results. Since duration of smoking is highly

Source: https://www.industrydocuments.ucsf.edu/docs/ptxk0000

correlated with age (r = .70), Cobb effectively restricts the analysis to young cancer patients and their controls who also have a relatively short history of smoking. Which then is the relevant variable, age or smoking duration? Undoubtedly they both are. And to interpret all differences in terms of one is quite misleading. Cobb's statement 'perhaps nighttime smoking just doesn't add much to the risk of lung cancer for those who have already smoked so long' could just as easily be written '... for those who have already lived so long.' The increased risk of cancer with increasing age has been well documented and occurs irrespective of physical carcinogens, such as tobacco, or 'psychologic factors' such as extreme repression and self-frustration....

"Both duration of smoking and nighttime smoking are associated with the incidence of cancer -- ie, more lung cancer patients smoke at night and have been smoking for a longer time. Duration and nighttime smoking are independent, suggesting that whether or not one smokes at night is unrelated to the total number of years that he has been smoking. The interaction is not significant: that is, the association between nighttime smoking and lung cancer does not differ significantly for the two duration periods ($\leq$ 35 years and $>$ 35 years)....

"The above points illustrate several important statistical and methodological concepts. Of course, the most important issue here is that whatever 'hunches' or hindsights an investigator has, he cannot selectively resample the sample or change the original hypothesis, except within the confines of allowable statistical procedures."

SEGERS, M.J. & MERTENS, Ch., Catholic University of Louvain, Belgium

"Anxiete, depression et risque d'atherosclerose des coronaires." (Anxiety, depression and the risk of coronary atherosclerosis) (Acta Psychiatrica Belga 72/1: 46-55, January 1972: authors' English summary plus partial translation)

"The authors have tried to evaluate in 507 unselected subjects, the discriminative risk value of depression and anxiety scales, as well as bioclinical measurements in coronary atherosclerosis. Results show that psychological factors favor coronary atherosclerosis. They also show that there is no linear relationship between psychological and bioclinical parameters....

"The mean of depression is significantly higher in the category of subjects who smoke more than 25 cigarettes per day as compared with the categories of subjects who don't smoke at all, those that smoke, but less than 10 cigarettes, and those that smoke between 10 and 25 cigarettes per day. It seems very probable that depression, at a certain level, impells the subjects to make abusive use of tobacco."

00236705 3

Source: https://www.industrydocuments.ucsf.edu/docs/ptxk0000

10. NICOTINE

MORRISON, C.F. & STEPHENSON, J.A., Tobacco Research Council Laboratories, Yorkshire, England

"The occurrence of tolerance to a central depressant effect of nicotine." (British Journal of Pharmacology 45: 151-56, September 1972)

"1. Rats were injected with 0.8 mg nicotine/kg, 0.8 mg amphetamine/kg or with saline immediately before being tested for 30 min in activity boxes.

2. During the first 3 trials the nicotine group were less active than the controls but from trial 5 onwards nicotine had a stimulant effect. The stimulant effect of the amphetamine did not alter with repeated injection....

"These experiments have demonstrated that rats developed a tolerance to the depressant effects of nicotine. This depended on the repeated administration of the drug and not on repeated experience of the experimental situation. Once the tolerance had developed it could, rather surprisingly, persist in the absence of further injections of nicotine. Nicotine has an initially depressant effect on barpressing behavior in the rat and this has been shown to be a central effect. It seems reasonable to assume that the depressant effect of nicotine on activity is also central, and the present results suggest a rapid adaptation to a central effect of nicotine. This may parallel the adaptation or development of tolerance to the unpleasant effects of smoking, such as nausea and sweating, experienced by the novice smoker....

"Nicotine has now been shown to increase, decrease or to have no effect on the activity scores of rats in activity boxes, depending on the animals' previous experience of nicotine. This could explain the apparent inconsistencies in the effects of nicotine on activity previously reported."

WEISS, G.B., Medical College of Virginia, Richmond

"On the site of action of nicotine in frog rectus abdominis muscle." (The Journal of Pharmacology and Experimental Therapeutics 183/1: 169-81, October 1972)

"Experiments were designed to elicit information about the cellular site of action of nicotine in frog rectus abdominis muscle. Nicotine (6.16 and 61.6 μM) increased muscle Ca retention after a subsequent 120-minute washout, decreased total Ca^{++} content and did not alter Ca loss when added during the slow component phase of the washout. Increasing pH from 6.80 to 9.40 increased nicotine-induced Ca retention and decreased the rate of development (but not the magnitude) of the contractile response. Procaine (3.67 mM), high K^+ (80 mM) and d-tubocurarine (25 μM) but not acetylcholine (ACh 2.3 μM) blocked contractions and increased Ca retention induced by nicotine, whereas nicotine blocked contractions elicited by ACh but not those obtained with high K^+. Hemicholinium-3 partially inhibited contractions and the increased Ca retention elicited by nicotine but did not affect similar actions of ACh. These results indicate that nicotine 1) acts at receptors at the neuromuscular junction and only a portion of these may be ACh receptors, 2) is active in both ionized and nonionized

4002367054

Source: https://www.industrydocuments.ucsf.edu/docs/ptxk0000

molecular forms and 3) does not exert these actions at sites beyond the neuromuscular junction. The varied responses obtained with either the ionized or nonionized forms of nicotine occur at similar extracellular concentrations. The importance of each of these stimulatory mechanisms in the evaluation of actions of nicotinic agents on frog rectus abdominis muscle is uncertain."

CRECELIU, V.H.-J. & FORWERG, W., Frankfurt on Main, West Germany

"Abscheidung von Nikotin-Aerosolen zur Bestimmung von Nikotin in Raumluft." (Separation of nicotine aerosols for the determination of nicotine in room air) (Zentralblatt fur Arbeitsmedizin und Arbeitsschutz 22/7: 200-3, July 1972: paraphrased English Abstract)

The authors had previously reported their development of a method for the measurement of nicotine in room air and in this report had described experiments showing that the method produced a quantitative (98%) separation of the nicotine vapor. However, a considerable proportion of the nicotine in cigar and cigarette smoke is present as a nicotine-containing aerosol, and in the present report the authors describe experiments to determine the degree of separation of the nicotine-containing aerosol obtained by this method. It was found that the mean degree of separation, using the same absorption solution as in the earlier studies (0.1 N sulfuric acid and 0.2% n-butanol), was at least 93%. The article contains diagrams and a detailed technical description of the apparatus used in this method.

11. SMOKE CONDENSATE AND CONSTITUENTS

HOFFMANN, D., RATHKAMP, G., NESNOW, S. & WYNDER, E.L., American Health Foundation, New York

"Fluoranthenes: Quantitative determination in cigarette smoke, formation by pyrolysis, and tumor-initiating activity." (Journal of the National Cancer Institute 49/4: 1165-75, October 1972)

"A method for the determination of fluoranthene in cigarette smoke was developed. The nonvolatile particulate matter of cigarette smoke was distributed between 2 solvent pairs, chromatographed on alumina, and the fluoranthene concentrate analyzed by gas chromatography, high-speed liquid chromatography, and paper chromatography. 9-^{14}C-phenanthrene and 9-^{14}C-benz[a]anthracene served as internal standards. The mainstream smoke of an 85-mm U.S. blended nonfilter cigarette contained 263 mg of fluoranthene, 116 ng of 1-, 3-, and 7-methylfluoranthene, 68 ng of 2- and 8-methylfluoranthene, and more than 100 ng of dimethylfluoranthenes. Pyrolysis experiments suggested that in cigarette smoke the fluoranthenes were partially formed via the Diels-Alder addition of acenaphthylenes with volatile dienes. Of the 5 possible monomethylfluoranthenes, 2- and 3-methylfluoranthenes were active as tumor initiators as were 2,3- and 7,8-dimethylfluoranthenes. 2-Methylfluoranthene was also active as a complete carcinogen....

"Although the initiating tumorigenicity of the active alkylfluoranthenes was significantly lower than that of BP, their higher total concentration in

00236705

Source: https://www.industrydocuments.ucsf.edu/docs/ptxk0000

cigarette smoke (approximately 80 ng/cigarette) than BP (30 ng/cigarette) suggests, nevertheless, that they contributed somewhat to the overall tumor-initiating activity of cigarette smoke condensate. At present, the lack of data on the tumor-initiating activity of several other PAH in tobacco smoke permits no quantitative information as to the importance of the contribution of alkylfluoranthenes to the carcinogenicity of tobacco tar."

BHALLA, P.R., KOCHHAR, T.S. & SABHARWAL, P.S., University of Kentucky, Lexington

"Induction of mitotic abnormalities in the root tips of allium cepa by tobacco smoke." (Experientia 28/9: 1122-3, September 15, 1972)

"Nakanishi et al. while working with human epithelial lung cells treated with cigarette smoke condensate observed a decrease in average chromosome number to 76, from a modal value of 77 for the chromosomes in untreated cells. This finding was attributed to the appearance of dicentric chromosomes in some of the passages. Bouchard and May observed an increased number of mitotic abnormalities in mouse lung fragments that had been bathed for 24 h in a smoke condensate solution. Later investigations also found that cigarette smoke condensate has profound influence upon mammalian cells. Yet with a very few exceptions which are perhaps best exemplified by chronic granulocytic leukemia in humans, the observed chromosomal anomalies commonly found in cancer cells show no consistent pattern. The present investigation is another approach used to ascertain the feasibility of utilizing plant tissues as a quick and sensitive bioassay for tobacco smoke. Vacuolization of the cytoplasm, pycnotic nuclei and other mitotic abnormalities were seen 24 h after exposure to cigarette smoke. Other mitotic irregularities include occasional 'stickiness' of chromosomes at metaphase and bridging at anaphase and telophase. Thus, the present investigation clearly demonstrates that one can detect similar cytological responses in plants and animals exposed to tobacco smoke. A study of tobacco smoke and its constituents on plant tissues might lead to a better understanding of their mechanism of action. We are currently investigating the effect of different subfractions of tobacco smoke and results will be reported subsequently."

0002367056

ALEXANDROV, K. & FRAYSSINET, C., Villejuif, France

"The effect of cigarette-smoke condensate on the in vitro fixation of benzo(a)pyrene on DNA." (Experientia 28/8: 932-3, August 15, 1972)

"Bonds between the carcinogen B(a)P and the DNA molecule are possible in vitro with certain metabolites of carcinogen produced by aryl-hydroxylase located in the microsomes. In our experiments the cigarette smoke condensate is a very strong inducer of the hepatic microsomal enzymes.

"Comparable results have been reported showing that the inhalation of cigarette smoke is capable of greatly stimulating the enzymatic oxydation of B(a)P in the lungs of rats. Phenomena of a similar order have been demonstrated in the placenta of pregnant women who smoke.

Source: https://www.industrydocuments.ucsf.edu/docs/ptxk0000

"The smoke condensate when incubated with the microsomes is also capable of forming complexes with DNA. A second incubation of the DNA-condensate complexes with the metabolites of B(a)P-3H results in a much lower rate of fixation of B(a)P.

"The cigarette smoke condensate contains benzopyrene but in quantities too weak to cause a direct intervention: 1 mg of condensate that inhibits fixation in the order of 60% does not contain more than 0.04% of B(a)P added in the middle of the incubation.

"In addition, we must admit that in the cigarette smoke condensate there are substances different to B(a)P that can occupy the specific sites of fixation of this B(a)P on the DNA molecule."

GARCIA, H. & LIJINSKY, W., University of Nebraska

"Tumorigenicity of five cyclic nitrosamines in MRC rats." (Zeitschrift fur Krebsforschung 77/4: 257-61, 1972)

"Five cyclic nitrosamines have been fed to groups of 30 MRC rats at a concentration of 100 mg/liter in drinking water. Nitroso-3-pyrroline produced only tumors of the liver, and was the weakest carcinogen of the five. Nitrosopiperidine induced tumors of liver, esophagus and respiratory tract. Nitrosomorpholine induced tumors of liver and the nasal cavity. Nitrosoheptamethyleneimine induced squamous tumors of lung, and tumors of the esophagus and trachea and was the most potent carcinogen of the five. Dinitrosopiperazine induced tumors of the nasal cavity. The reasons for the pronounced organ specificities of these nitrosamines are discussed."

12. PREVENTIVE MEDICINE

[The journal, Preventive Medicine, August 1972, is a special "Forum Issue on Cancer." Many of the articles make passing reference to cigarette smoking. However, only the three given below were considered of sufficient interest to be abstracted.]

WYNDER, E.L. & MABUCHI, K., American Health Foundation, New York

"Etiological and preventive aspects of human cancer." (Preventive Medicine 1/3: 300-34, August 1972)

"There are only two ways to achieve the prevention of cancers associated with smoking: Do not smoke; manufacturs less tumorigenic tobacco products.

"The first means is clearly based on the individual decision. In order to provide a larger number of people with a motive to stop or not to start smoking, a continuing campaign to inform the public of the hazards of smoking is needed. The results of such a campaign are more likely to be fruitful if it is aimed at young people who have smoked only for a short while or who have not started smoking. In order to assist people who wish to stop smoking, the establishment of large numbers of smoking withdrawal clinics will be required. It is to be hoped that in the future every hospital will have an anti-smoking clinic as part of its health care facility.

00236705?

Source: https://www.industrydocuments.ucsf.edu/docs/ptxk0000

"In view of the accumulation of evidence indicating the value of developing less harmful cigarettes, the second means of prevention seems of special promise remembering that historically the great advances in preventive medicine were usually not based upon what an individual did for himself but rather what society did in terms of changing the product or the environment."

BELLOC, N.B. & BRESLOW, L., California State Department of Health, Berkeley

"Relationship of physical health status and health practices." (Preventive Medicine 1/3: 409-21, August 1972)

"This paper examines the relation between common health practices, including hours of sleep, regularity of meals, physical activity, smoking and drinking, and physical health status. Good practices are shown to be associated with positive health, and the relationship of these activities was cumulative; those who followed all of the good practices being in better health, even though older, than those who failed to do so. This association was found to be independent of age, sex, and economic status....

"In view of the extensive evidence on the relation between smoking and health, it is not surprising to find in Table 5 that those who had never smoked enjoyed better physical health than present or past smokers. The differences in physical health status, as measured by the PHR, relative to cigarette smoking are not as large as in the case of some other health practices. Men who had never smoked scored .47 compared with .51 for present and past smokers. Whether one inhales cigarette smoke and the extent of such inhalation appears highly correlated with physical health status."

WEBER, K.H., Hamburg, Germany

"Tar and nicotine in German cigarettes." (Preventive Medicine 1/3: 446-50, August 1972)

"During the past 15 years systematic measures of the German cigarette industry and a remarkable change in smoking habits in the Federal Republic of Germany have considerably reduced the per capita exposure to cigarette smoke. To achieve this goal, manufacturers have combined careful tobacco selection and the early introduction of filter cigarettes with several important technological improvements such as the continuous modification of cigarette filters, the finer cut of cigarette tobaccos, the improvement of paper porosity and the increasing use of homogenized tobacco leaf. Smokers have not only accepted these gradual changes, they have promoted this development by changing their smoking habits, e.g., smoking cigarettes down to longer butt lengths....

"1. Although cigarette consumption has increased by 37% it can be shown that the total intake of smoke condensate and nicotine per capita and per smoker has decreased by as much as 27% (condensate) and 20% (nicotine) in the Federal Republic of Germany between 1961 and 1970.

"2. During the last ten years a smoker who has not increased his daily consumption and who has followed the general tendency towards leaving long butts has, on the average, decreased his intake of condensate and nicotine by as much as 40%.

2023677058

Source: https://www.industrydocuments.ucsf.edu/docs/ptxk0000

"3. While per capita cigarette consumption has increased during the last ten years, there has been a marked reduction in the consumption of cigarette smoke.

"Very surprisingly, few studies about such developments have been published. Therefore, it seems highly desirable to collect more data of this type and use such information as a base for future research concerning the epidemiology of smoking and health."

REED, C.S., Sydney Hospital, Australia

"Are multiphasic health screening programmes a desirable innovation?" (The Medical Journal of Australia 2: 1018-24, October 28, 1972)

"The preventative aspects of coronary artery disease are looked into by clinical estimations of blood pressure, blood sugar levels, serum uric acid levels and serum cholesterol levels. Despite the known need for further projected data in heart disease detection (and it is claimed that these records will be useful for prospective studies), there has only been discussion of providing estimations of serum levels of triglycerides and lipoprotein electrophoreses, without which no competent physician feels at ease.

"Thus Ancel Key's study (1970) of 'Coronary Heart Disease is Seven Countries' made it clear that the so-called risk factors cannot explain differences in coronary heart disease in different countries. The so-called 'risk factors' include: (i) cigarette smoking; (ii) occupational and physical activity; (iii) body fatness and weight.

"There is a tendency for blood pressure and coronary heart disease to be linked, and overall the strongest relationships concern the percentage of men with serum cholesterol values over 250 mg/100 ml and the amount of dietary saturated fatty acids.

"However, despite this, Cochrane's (1970) ten-year study in the United Kingdom shows that serum cholesterol level, body weight or cigarette smoking does not correlate with mortality; only blood pressure shows his correlation."

13. OPINIONS

JOHNSTON, L., United Kingdom

"Craving for tobacco." (Letter: Lancet II: 981, November 4, 1972)

"As an explanation of the operation of the craving for tobacco the vicious circle hypothesis, smoking⇆craving, though commendably concise, does not take account of all the facts.

"When a confirmed smoker stops smoking, what produces the unpleasant sensation, craving, is not, I think, known. It may be assumed, however, that whatever it is -- Let us call it C -- is produced by repeated smoking -- i.e., repeated doses of nicotine -- and that it is stored, probably, in the central nervous system. Soon after a smoke, the release of C from the store

00236705

Source: https://www.industrydocuments.ucsf.edu/docs/ptxk0000

commences, and when enough has been released to produce a certain level of craving, the smoker smokes again. If, however, he stops smoking, C continues to be released and to punish the smoker until either he re-starts smoking, or until the store of C, accumulated usually over years, runs out."

SOMMER, R.M., Redondo Beach, California

"Nonspecification of tobacco smokers." (Letter: Journal of the American Medical Association 222/4: 487, October 23, 1972)

"In the July 31 issue of The Journal, Dr. Daniell discussed the relationship between osteoporosis and smoking. The letter appeared to be well documented and convincing, but the theory is far from flawless. I am an ex-smoker and, like Dr. Daniell, am always searching to connect disease processes with the deleterious effects of smoking.

"Nevertheless, smokers and nonsmokers are different people, so they cannot be used as comparable study groups. Those who do not smoke for reasons of healthy living habits, also carry these living habits into sports activities, proper diet, etc, all of which contribute to a positive calcium balance and less osteoporosis. Furthermore, heavy smokers as a group do not force themselves to do regular exercise to a like extent, and are less likely to be capable of equivalent physical exertion, due to a higher incidence of cardiovascular and respiratory disease in this smoking group."

RAZANSKI, J.J., New York

"Osteoporosis and smoking." (Letter: Journal of the American Medical Association 222/7: 838, November 13, 1972)

"I wish to respond to Dr. Daniell's letter published in the July 31, 1972, issue of The Journal regarding the relationship between osteoporosis and smoking....As is well known, severe immobility can lead to osteoporosis. Decreased osteoblastic and increased osteoclastic activity occurs as a result of immobilization and lack of proper mechanical stress on bones. In Dr. Daniell's study, the group with idiopathic pre-senile osteoporosis included many subjects with severe chronic respiratory illnesses. Two of the patients died subsequently of chronic obstructive pulmonary disease. Thus, in this study, heavy smoking seems as likely to be related to osteoporosis via severe respiratory illness causing immobility as via the other mechanisms proposed to explain the findings.

"In rehabilitation medicine, severely immobilized patients are prevented from developing osteoporosis by tilt table therapy that gradually places proper mechanical stresses on the skeleton. Perhaps such treatment would be of benefit for certain patients with severe immobilizing respiratory diseases."

00236706O

Source: https://www.industrydocuments.ucsf.edu/docs/ptxk0000

14. BRIEFS FROM MEETINGS

American Heart Association, Dallas, November 16-19, 1972

The following numbered abstracts appeared in Circulation 46/4: October 1972, Supplement II.

GARCIA-PALMIERI, M., COSTAS, R., GORDON, T., KAGAN, A., KANNEL, W.B. & SCHIFFMAN, J., Puerto Rico Heart Health Program, San Juan

"Differences in coronary heart disease in Honolulu, Puerto Rico and Framingham." (375)

"Carefully standardized objective evidence of the prevalence and incidence of coronary heart disease (CHD) is now available for representative populations of men 45-64 in Framingham, Puerto Rico and among Honolulu Japanese. The prevalence of electrocardiographic evidence of myocardial infarction (MY by ECG) and the incidence of CHD (MI by ECG plus CHD death) in Puerto Rico and in Honolulu Japanese is half that in Framingham. A large number of population characteristics were compared. While serum cholesterol levels and amount of cigarette smoking are lower in Puerto Rico and Honolulu than Framingham, and blood pressure levels are nearly the same, these facts (individually or in combination) do not account for all the differences in CHD incidence or prevalence. These unexplained differences suggest the need for extending research to new areas than usual risk factors."

SPAIN, D.M., SIEGEL, H. & BRADESS, V., Brookdale Hospital Medical Center, New York

"Smoking habits and sudden death from coronary disease in women." (376)

"Smoking habits and sudden and unexpected death (S.D.) as the initial clinical event in coronary disease was studied in 181 medical examiner autopsied cases in women. 46% (84) were nonsmokers (N.S.), 20% (36) were light smokers (L.S.), and 34% (61) were heavy smokers (H.S.). Of the 29 S.D. from coronary disease, there were 10% (3) N.S., 28% (8) L.S., and 62% (18) H.S. The mean ages for this latter group were 67, 55, and 48 respectively. The male to female ratios of coronary S.D. as related to smoking habits in the N.S. were 11-1 (32-3), in the L.S. 4-1 (31-8) and in the H.S. 3.5-1 (62-18). Comparing the male to female ratios of coronary S.D. in those less than age 51 revealed a ratio of 12-1 (183-15) during 1949-1959, and a ratio of 5-1 (55-11) during 1967-1971. The close association of H.S. with coronary S.D. in young women, the markedly lower mean age at which this occurs, and the relative increase in the coronary S.D. in women as compared to men in the recent period which corresponds the increase in H.S. among women, strongly support H.S. as an important risk factor in S.D. from coronary disease."

2002367061

Source: https://www.industrydocuments.ucsf.edu/docs/ptxk0000

NOBREGA, F.T., OXMAN, H.A., CONNOLLY, D.C., ELVEBACK, L.R., TITUS, J.L. & KURLAND, L.T., Mayo Clinic, Rochester, Minnesota

"The high risk patients with angina pectoris." (378)

"With the increasing availability of diagnostic and therapeutic measures for patients with clinical ischemic heart disease (IHD), it has become important to identify patients at highest risk for cardiac death (CD) and subsequent myocardial infarction (MI) who might benefit most from the use of these measures. As part of a study of IHD among residents of Rochester, Minnesota, the medical records of all residents who had classical angina pectoris (CAP) as their initial manifestation of IHD were reviewed for the presence of prior risk factors. By means of stepwise discriminant analysis it was possible to determine that the most important factors for CD were: (1) cardiac enlargement by chest x-ray (2) diastolic hypertension (3) cigarette smoking (4) an abnormal resting electrocardiogram at the time of diagnosis of CAP and (5) an elevated cholesterol level. Using these variables and CD as the endpoint, we were able to correctly classify 92% as living and 75% as dead at five years. With these same variables, we were also able to accurately classify which patients were at highest risk for developing a MI within five years after the initial diagnosis of CAP. Using combinations of these variables we have been able to develop a risk profile for patients with CAP. Until the efficacy of the new surgical procedure is firmly established, these high risk factors should be considered in the selection of angina patients for early diagnostic and therapeutic intervention."

AHMED, S.S., MOSCHOS, C.B. & REGAN, T.J., New Jersey Medical School, Newark

"Cardiovascular effects of chronic smoking in beagles." (409)

"Chronic tobacco smoking has been associated with circulatory disorders, but the response separated from other risk factors has not been characterized. One year old litter mate beagles after permanent tracheostomy, were divided into seven controls, nine smoking 7 cigarettes/day and six receiving nicotine, 840 μg/kg i.m. After nearly two years the animals were catheterized under anesthesia for assessment of left ventricular function and volumes (indicator dilution). While heart rate, stroke volume, LV end-diastolic pressure and volume did not differ significantly in three groups, smokers had high systolic (153$\pm$ 6.6 vs 122$\pm$7 mm. Hg $P<0.01$) and diastolic pressures (109$\pm$4 vs 76$\pm$3.7, $P<0.001$). Diminished contractility was manifested by a reduced ejection fraction of 34.7$\pm$3 (vs 44$\pm$2.6% in normals, $P<0.005$) and the Frank-Levinson index of 1.41$\pm$0.12 (2.41$\pm$0.2 in normals, $P<0.05$). Reduction of arterial pressure to normal with hemorrhage did not alter these indices suggesting independence of afterload. Nicotine animals behaved similar to smokers, with markedly elevated peripheral resistance. Thus, both the arterial system and myocardium are affected at a level proportionate to cigarette usage in man."

00236706

Source: https://www.industrydocuments.ucsf.edu/docs/ptxk0000

MANDEL, W.J., LAKS, M.M., HAYAKAWA, H. & McCULLEN, A., Cedars-Sinai Medical Center, Los Angeles

"Alterations of the hemodynamic effects of nicotine by autonomic blockade in the conscious dog." (746)

"Previous investigations using in vitro preparations or anesthetized partially intact animals demonstrated the complex cardiovascular effects of N. The purpose of this study was to define more clearly the effects of N in a preparation resembling the normal physiological state. In the conscious dog, N 10-600µg was injected into the right atrium (RA), during continuous right ventricular (RV), pulmonary artery (PA) and aortic (A) pressure monitoring. At 400µg, a triphasic response occurred: 1) 2-4 sec sinus arrest followed by bradycardia 2) subsequent sinus tachycardia and marked increase in A, RV systolic and diastolic pressure 3) subsequent bradycardia and gradual return to control pressures. However, RVedp remained elevated for 10-30 min. Arterial injections of 10-600µg, demonstrated: 1) No sinus arrest 2) more pronounced pressure elevations at lower dosage 3) secondary bradycardia. Atropine (0.025mg/Kg IV) eliminated the sinus arrest following RA injection. Propranolol (1.0mg/-Kg IV) diminished the secondary cardioacceleration and slightly diminished the pressure responses. It is concluded that, in the conscious dog, N: 1) a) releases acetylcholine in the RA, b) may depress myocardial function 2) subsequently releases catecholamines 3) lastly produces a reflex bradycardia."

PAFFENBARGER, R.S., Jr. & WING, A.L., California Department of Public Health, Berkeley

"High-risk factors common to coronary heart disease and adult-onset diabetes mellitus." (797)

"Of 27,000 college alumni from Harvard and the University of Pennsylvania who responded to mail questionnaires, 852 reported doctor-diagnosed coronary heart diseases (CHD) and 362 doctor-diagnosed adult-onset diabetes mellitus (DM), while 33 reported both diseases, 16-52 years after college entrance. Validation procedures suggested these findings were within acceptable limits. Student physical and social records identified high-risk factors of CHD and DM common to both and suggesting similarities in their etiologies. Age at college case-taking and interval of followup were held constant in computing incidence rates of CHD and DM to identify high-risk factors. Chief among factors associated with increased risk of CHD were 1) cigarette smoking, 2) higher levels of systolic and diastolic blood pressure, 3) physical inactivity, 4) heavier weight for height, 5) shorter body stature, 6) sense of exhaustion, and 7) early parental death. These factors also were associated with increase risk of DM except 1) cigarette smoking, 2) diastolic blood pressure, 3) physical inactivity, and 4) body stature. On the other hand, reduced vital capacity and dyspnea on exertion were forerunners of DM but not of CHD. Similarities and differences in high-risk factors of CHD and DM may identify appropriate avenues of intervention for each disease."

002367063

Source: https://www.industrydocuments.ucsf.edu/docs/ptxk0000

RILEY, C.P., OBERMAN, A. & JONES, W.B., University of Alabama

"Angina pectoris in women." (837)

"Epidemiologic studies of coronary heart disease have shown a better life-expectancy for women than men with angina pectoris (AP). This study examines the diagnosis of typical, exertional AP, relieved by rest or nitroglycerin within five minutes, in patients having coronary arteriography (CAG). Coronary lumen stenosis of $\geq$ 50% in any vessel was considered an abnormal CAG. Of 134 patients with AP and CAG, 109 were men and 25 were women. A significantly higher rate of normal CAG was found in women (32%) than men (13%) ($p < .05$). No significant differences were found between women with AP and a normal CAG or an abnormal CAG for the following factors: age, systolic and diastolic blood pressures, smoking habits, serum cholesterol and triglyceride, and body weight.

"Normal CAG does not exclude a cardiac origin for AP; however, the presence or absence of major coronary lesions seriously affects prognosis. Although the number of patients studied is small, women with coronary artery disease have fared no better than men during a two-year follow-up period. The better life-expectancy of women than men with AP in epidemiologic studies may result from inclusion of many women without major coronary lesions."

SCOTT, R.A., HENSON, D.E., LESAK, A.E. & HASS, G.M., St. Luke's Medical Center, Chicago

"Relations between plasma free fatty acids and occurrence of calcific arteriosclerotic thromboarteritis in rabbits." (864)

"A regimen involving simultaneous use of nicotine, vitamin D and dietary cholesterol in rabbits resulted in a high incidence of peripheral calcific arteriosclerosis often complicated by thrombosis. Among 48 animals there was a positive correlation between the magnitude of nicotine-induced rise in plasma FFA and development of arterial disease. Calcific arteriosclerosis with thrombosis occurred in those (27) in which the rise exceeded 100%. Calcific arteriosclerosis without thrombosis occurred in those (13) in which the rise was about 50%. No arterial disease occurred in those (8) in which nicotine induced no rise in plasma FFA. When adrenalin was substituted for nicotine the rise in plasma FFA resembled that due to nicotine but only 4 of 15 developed arterial calcification. When nicotine was replaced by ACTH or heparin the rise in plasma FFA greatly exceeded that caused by nicotine and no animals developed arteriosclerosis or thrombosis. Hence the magnitude of rise in plasma FFA, as such, had no pathogenetic role in induction of peripheral arteriosclerotic thrombosis."

0002367064

SELTZER, C.C., Harvard School of Public Health, Boston

"Does it help to stop smoking?" (867)

"It is the present conventional wisdom that a decrease in cigarette smoking will result in a substantial decline in population death rates. It is based essentially on the oftentimes intermediate position of the death

Source: https://www.industrydocuments.ucsf.edu/docs/ptxk0000

rates of ex-smokers relative to those of continuing cigarette smokers and nonsmokers. However, such a conclusion ignores the fact that ex-smoker data often give contradictory and inconsistent findings and pose a virtually insoluble problem as to valid interpretations that may be drawn from such data in the present study design. Apart from ex-smoker data, cohort data in which there has been a substantial decrease in cigarette smoking over time present a more direct opportunity to view possible changes in death rates. Just such data are available from Doll and Hill's British doctors study which shows about a 50% decline in doctors smoking cigarettes from 1951 to 1966. Yet, over the same period, there is essentially no change in the death rates of these same British doctors. The absence of correspondence between the death rates among British doctors from 1951 to 1966 and their simultaneous downward trend in cigarette smoking, is strong refutation of the claim by the Public Health Service and others in medicine that stopping smoking increases the expectation of life."

SHINE, K.I., University of California, Los Angeles

"Contractile calcium in cardiac muscle: Observations with nicotine and quinine." (876)

"Nicotine and quinine effects upon mechanical function and ^{45}Ca exchange were investigated in the isolated perfused rabbit interventricular septum. Nicotine transiently increased developed tension and dP/dt without changing resting tension. Reserpine administration decreased but did not abolish the inotropic response to nicotine and did not facilitate a change in resting tension. No contracture was induced by 20 mM nicotine during zero calcium perfusion.

"0.1-2.0 mM of quinine reversibly depressed tension while 5.0-20 mM induced a contracture reaching 60% of twitch tension in the presence of 1.5 mM Ca. 5-20 mM quinine induced a phasic contracture during zero calcium perfusion averaging $29.4 \pm 1.8\%$ of twitch tension in blood perfusate and $22.5 \pm 3.4\%$ in HEPES buffer. 200 uM lanthanum reduced this contracture to $14.3 \pm 3\%$, but did not prevent it nor did this concentration of lanthanum prevent contracture when calcium perfusion was resumed. No effect upon ^{45}Ca uptake or efflux could be demonstrated during exposure to nicotine or quinine.

"The contractile apparatus in rabbit ventricle was activated by 5-20 mM quinine but not by nicotine in the absence of extracellular calcium. This may result from release of a quinine sensitive intracellular pool of calcium."

HASS, G.M., SCOTT, R.A., McCLAIN, E.D. & HENSON, D.E., St. Luke's Medical Center, Chicago

"Inhibition of nicotine-induced calcific arteriosclerotic thromboarteritis in rabbits by adrenalectomy." (991)

0002367065

"Rabbits on specific regimens of dietary cholesterol, vitamin D or nicotine developed no peripheral arteriosclerosis. When these regimens were combined in a group of 48 rabbits, 27 developed calcific arteriosclerosis

Source: https://www.industrydocuments.ucsf.edu/docs/ptxk0000

with thrombosis, 13 had arteriosclerosis without thrombosis and 8 had no arterial disease. The vasculo-toxic effects were not reproduced by the substitution of adrenalin for nicotine nor were they minimized by use of reserpine. Nineteen animals from which a sufficient amount of adrenal tissue had been removed did not develop peripheral arteriosclerosis or thrombosis. As a rule this required surgical removal of the left adrenal and cryogenic ablation of about two-thirds of the right adrenal with a residual after four months of not more than 250 mg of the regenerated right adrenal. Whether prevention of arteriosclerotic thrombosis was due to reduction of adrenal cortical or medullary function is not clear."

Central Society for Clinical Research and the Midwest Section, American Federation for Clinical Research, Chicago, November 2, 1972.

The following abstracts appeared in Clinical Research 20/4: October 1972 on the pages indicated.

SOLOMON, T.E., SOLOMON, N., SHANBOUR, L.L. & JACOBSON, E.D., University of Texas, Houston

"Direct effect of nicotine on exocrine pancreatic secretion." (p. 735)

"We have previously reported inhibition of pancreatic secretion of water and bicarbonate by nicotine in dogs and by cigarette smoking in man; this inhibition of intraduodenal neutralizers of gastric acid may be the link between cigarette smoking and duodenal ulcer disease. We investigated the mechanism of pancreatic inhibition by nicotine. An in vitro preparation of the rabbit pancreas was used in which the organ was suspended in Krebs solution and gassed with 95% O_2-5%CO_2. The main pancreatic duct was cannulated to collect spontaneously secreted juice comparable in amount and composition to in vivo secretion. Addition of nicotine (10 mM) to the bath for 1 hour caused highly significant reductions of 33±8.0% in volume, 13±2.1% in bicarbonate concentration, and 39±6.0% in bicarbonate output (values expressed as percent change between nicotine hour and preceding control hour; n=6; there was no significant difference between comparable hours in a separate control series of 4 experiments). In 6 anesthetized rabbits, smoking doses of nicotine (100 to 400 µg/kg-hr, i.v.) also inhibited spontaneous secretion: decreases of 23±6.3% in volume and 31±5.8% in bicarbonate output were seen (data presented as for in vitro above; all p values for in vitro and in vivo data less than 0.01). It appears that nicotine inhibits exocrine pancreatic secretion of water and bicarbonate by direct effect on cellular mechanisms."

FALK, L., DEINHARDT, F. & WOLFE, L., St. Luke's Medical Center, Chicago

"Transformation in vitro of nonhuman primate lymphocytes by Epstein-Barr virus." (p. 793)

002367066

"Epstein-Barr virus (EBV), a herpes-type virus, causes infectious mononucleosis (IM) and has been implicated as the etiologic agent of Burkitt's lymphoma (BL) and nasopharyngeal carcinoma (NPC). Lymphocytes from IM patients and cells from BL and NPC frequently yield lymphoblastoid cell lines after cultivation and EBV is always associated with these cell lines.

Source: https://www.industrydocuments.ucsf.edu/docs/ptxk0000

"Peripheral squirrel and marmoset lymphocytes (recipients) were transformed in vitro into lymphoid cell lines after cocultivation with lethally irradiated (6000 r), EBV-carrying human lymphoid cells (donor). The monkey lymphocytes became established as cell lines after 25-35 days of cultivation; donor and recipient lymphocytes, cultured separately, failed to form cell lines. Chromosomal analyses of the cell lines revealed normal diploid squirrel monkey and marmoset karyctypes. EBV antigens were demonstrated in the monkey cell lines by immunofluorescent staining. These results confirm and extend previous reports of transformation by EBV of lymphocytes from squirrel monkeys and marmosets (Miller et al. PNAS 69: 383, 1972) and gibbons (Henle, personal communication). Despite the proven susceptibility of marmosets to various oncogenic viruses, experimental infection with EBV has not succeeded, but attempted infection with EBV transformed autologous lymphocytes has not been investigated. The transformed lymphocytes have been inoculated into the autologous monkeys and their clinical and immunological responses were studied."

BROUN, G.O., Sr., SWEET, H.C., KINSELLA, P.W., SCHMIDT, R.R. & PUDER, B., St. Louis University, Missouri

"Factors affecting data on prevalence of pulmonary emphysema." (p. 805)

"Knowledge of past incidence of chronic obstructive pulmonary disease (COPD) is essential to establish the role of smoking, air pollution and respiratory infections in its epidemiology. The diagnostic terms, emphysema, chronic bronchitis and asthma are used irregularly and the true incidence of COPD is more closely reflected in combined data on these conditions. Recorded U.S. mortality attributed to emphysema increased markedly from 1950 to 1968. In the University Hospital a study of COPD began in 1947 and a pulmonary laboratory was established in 1950. A marked increase in admissions for COPD occurred after 1948, reaching a maximum in 1959. A treatment program involving reduction in smoking, use of bronchodilators, inhalation therapy, and treatment of respiratory infections was followed by a definite reduction in COPD admissions and mortality so that by 1969-1970 the level approaches that of 1949-1950. In other hospitals where no similar study program existed and where a pulmonary laboratory was established at a later date an increase in COPD admissions occurred after the laboratory became operative and a definite peak has not yet been reached. The date of onset of chronic cough in individuals later observed with COPD provides information not dependent on laboratory studies. It provides a rough estimate of the time when factors causing bronchial irritation became operative. Our data indicate that this occurred in the late 1940's and early 1950's. Only pulmonary function studies show the true incidence of COPD."

CANTRELL, E., MARTIN, R., WARR, G. & SHAW, C., M.D. Anderson Hospital, Houston

"Aryl-hydrocarbon hydroxylase induction in human alveolar macrophages." (p. 805)

"Aryl hydrocarbon hydroxylase (AHH) is an inducible membrane-bound microsomal enzyme found in many tissues throughout the body. Because

0023267

Source: https://www.industrydocuments.ucsf.edu/docs/ptxk0000

cigarette smoke contains potential carcinogens such as 3-methylcholanthrene and benzpyrene, the degradation of these polycyclic hydrocarbons by lung cells is of particular importance. Levels of AHH were measured fluorometrically in pulmonary alveolar macrophages (PAMS) obtained by saline pulmonary lavage from healthy volunteers who were either smokers or nonsmokers. AHH levels were low in PAMS from 7 nonsmokers, with a mean (+SE) activity of .008 ± .003 units (1 unit = 1 picomole hydroxybenzpyrene/min/10^6 cells). PAMS from 6 healthy volunteers who regularly smoke from 10 to 20 cigarettes per day contained higher AHH levels with a mean level of .15 ± .04 units ($P < .001$). AHH induction was studied in PAMS from serial lavages performed on a healthy 29 yr. old male volunteer who had not smoked cigarettes for six years previously. AHH activity was .010 and .009 units in PAMS from 2 control lavages 4 months apart. One week after smoking resumed, the level of AHH rose slightly to 0.13 units. By 30 days, however, AHH activity had increased three-fold to .041 units. These studies indicate that AHH is inducible in vivo in PAMS by cigarette smoking. These actively phagocytic cells may serve as a first line of defense in the lungs to protect the body from potentially carcinogenic chemicals in cigarette smoke."

SWEET, H.C., BROUN, G.O., SR., KINSELLA, P.W. & PUDER, B., St. Louis University, Missouri

"Smoking as a factor in the development of emphysema." (p. 809)

"Many reports indicate that cigarette smoking is a major factor in the development of chronic obstructive pulmonary disease (COPD) the pathology and clinical history of which resembles the development of pneumoconiosis. To determine whether there is an increase of severity of COPD associated with progressively more cigarette smoking, the smoking history of 1200 patients who have had pulmonary function tests has been correlated with the severity of pulmonary function impairment. Smoking history was evaluated by pack years, i.e. one pack per day for one year equals one pack year.

"Nonsmokers show the least amount of impairment but 14% of the nonsmokers tested showed evidence of COPD.

"One out of five people who have smoked twenty pack years have severe COPD and over 50% of those who have smoked over forty pack years show moderate to severe emphysematous change.

"A marked increase in cigarette consumption in the U.S.A. began in 1941. In 1600 cases of COPD the time of onset of chronic cough was recorded. Cases with chronic cough increase strikingly after 1943 and the two curves closely parallel one another for more than 10 years.

"Tobacco, however, can not be the only factor in the development of COPD since there is a small but significant group of nonsmokers who develop the disease and some individuals maintain normal pulmonary function even after more than forty pack years of smoking."

2002367068

Source: https://www.industrydocuments.ucsf.edu/docs/ptxk0000

Annual Clinical Congress, American College of Surgeons, San Francisco, October 1972

The following news report appeared in Medical Tribune 13/42: 1, November 1, 1972.

FRALEY, E.F., ELLIOT, A.Y., HAKALA, T.R., CASTRO, A.E. & CLEVELAND, P., University of Minnesota

"Human cancers: An RNA virus held isolated."

"A propagatable RNA virus has been isolated directly from a series of human cancers.

"Dr. Elwin E. Fraley, chief of the division of urology at the University of Minnesota Medical School, reported to the American College of Surgeons here that the virus, tentatively named EFMU-1, was found in the surgical specimens or primary tumor cell cultures of four successive adult male patients with tumors of the urothelium who were extensively studied....

"While not yet ready to term the virus oncogenic, Dr. Fraley noted that 'this virus very closely resembles viruses that are known to produce cancers in animals....'

"Dr. Fraley refused to comment about any attempts to test infectivity of the virus in animals.

"All four patients with the transitional cell tumor, found in the lining of the renal pelvis, and the virus had antibodies to that virus. Antibody formation was not seen in age-matched controls of 12 patients without cancer or some 20 patients with other types of tumors....

"At best, oncogenicity of the EFMU-1 virus in man, Dr. Fraley observed, can be shown only indirectly. Since it is an RNA virus, 'it theoretically should be susceptible to chemotherapy' of the sort that affects other RNA viruses. Viral etiology, he said, will be proved when 'the virus is eliminated by chemotherapy and the course of the disease is altered.'"

15. ADDITIONAL REFERENCES

AD HOC BLADDER CANCER COMMITTEE OF THE CCIRC, "Tumors of the bladder," J. Urology 108/3: 414-8, Sept 1972. (Smkg habits, occupation, geography, diet in id. hi risk grps)

AMERICAN CANCER SOCIETY, "The dangers of smoking - The benefits of quitting," Booklet publ. October 1972, 48pp.

ASAHINA, S. et al (Cleveland), "Carcinogenicity of organic fractions of particulate pollutants collected in New York City and administered subcutaneously to infant mice," Ca Research 32/10: 2263-68, Oct. 1972

BACH, W. & LENNON, K. (Hawaii), "Air pollution and health at Ala Moana Shopping Center in Honolulu," Hawaii Med J 31/2: 104-13, March-Apr 1972

00236706

Source: https://www.industrydocuments.ucsf.edu/docs/ptxk0000

BARNES, R. (Australia), "Asbestos and malignant disease," Med J Aust 2: 1107-13, Nov. 11, 1972, (Pts. who died from bronchogen. ca. were med. to heavy smkrs)

BERGER, H. & SCHWEIGLER, M. (Staten Is.), "Smoking characteristics of methadone patients," Letter: JAMA 222/6: 705, Nov 6, 1972, (98% of pts smk)

BLUMER, W. et al (Switzerland), "The cancer risk from traffic," Z. Praventivmed. 17/3: 157-61, May-June 1972. (9 Xs hi'er in those living along mainroad. See page 6 this issue CD)

BOITEAU, H.-L. et al (France), "Polycyclic hydrocarbons in various materials containing asbestos," Arch Mal Prof 33/6: 261-70, June 1972 (Third of asbestos samples had carcinogen. compounds)

BRAUN, P. (France), "Les super-vieillards de l'equateur," Rev Gerontol Express Fr No. 2: 59-62, Apr 1972. (People of great age living in Vilcabamba smoke consid amt tob w/out bad effects)

BUCCIARELLI, E. & RIBACCHI, R. (Italy), "C-type particles in primary and transplanted lung tumors induced in BALB/c mice by hydrazine sulfate: Electron microscopic and immunodiffusion studies," JNCI 49/3: 673-84, Sept 1972. (CTR-grant)

BURBANK, F. & FRAUMENI, J.R., Jr. (NCI), "U.S. cancer mortality: Nonwhite predominance," JNCI 49/3: 649-59, Sept 1972. (Nonwhites more exposed or vulnerable to carcinogen fact.)

BUSBEE, D.L. et al (Texas), "Aryl hydrocarbon hydroxylase induction in human leukocytes," Science 178: 315-6, Oct 20, 1972. (method described)

BUSH, L.P. et al (U Ky), "Influence of puff frequency and puff volume on the alkaloid content of smoke," J Agric Fd Chem 20/3: 676-8, 1972. (Alk content incr w incr puff vol, freq)

CHEN, H.W. et al (Jackson Lab/NCI), "Tumorigenesis in Strain DW/J mice and induction by prolactin of the group-specific antigen of endogenous C-type RNA tumor virus," JNCI 49/4: 1145-54, Oct 1972.

CHITNIS, M.P. et al (India), "Anti-cancer activity of the extracts of stem and leaf of Tylophora indica," Ind J Med Res 60: 359-62, March 1972.

CONNEY, A.H. & BURNS, J.J., (New Jersey), "Metabolic interactions among environmental chemicals and drugs," Science 178: 576-86, Nov 10, 1972. (Incl BP metabol in c'ette smkrs)

CREAGAN, E.T. & FRAUMENI, J.F. (NCI), "Cancer mortality among American Indians, 1950-67," JNCI 49/4: 959-67, Oct 1972, (Mort from all neoplasms combined signif lower than expected)

CROWDY, J.P. & LEWTHWAITE, C.J. (England), "Smoking habits of young soldiers. A comparison between 1959 and 1966 Generations," J Roy Army Med Corps 118/3: 168-72, July 1972. (w/in age grps 16-18, a signif. fewer reg smkrs in 1966 but greater than civilian pop)

DALY, M.B. & TYROLER, H.A. (U N.C.), "Cornell medical index response as a predictor of mortality," Brit J Prev Soc Med 26: 159-64, Aug 1972.

00236720

Source: https://www.industrydocuments.ucsf.edu/docs/ptxk0000

ECKHART, W. (Cal), "Oncogenic viruses," Ann Rev Biochem 41: 503-17, 1972.

FEHR, K.O. & KALANT, H. (U. Toronto), "Analysis of cannabis smoke obtained under different combustion conditions," Can J Physiol Pharmacol 50/8: 761-8, August 1972. (Synthetic THC appl to tob c'ettes less completely recovered. Tar content of canab smoke greater than tob smoke)

FEINSTEIN, A.R. (Yale), "Clinical biostatistics. XVIII. Synchroncus partition and bivariate evaluation in predictive stratification," Clin Pharmacol Ther 13/5: 755-68, Sept-Oct 1972.

FINGERLAND, A. (Czech), "Half of infarction deaths linked to smoking," Med Trib 13/43: 3, Nov 8, 1972.

FORBES, A.J. (Australia), "Three of four smokers believe habit is harmful, survey finds," Med Trib 13/43: 2, Nov 8, 1972.

FREJAVILLE, J.-P. (France), "Manipulation de feuilles de tabac," Concours Med 94/15: 2892, Apr 8, 1972. (Q & A: Farmer w. nausea, vomiting & abdom pain during tob sorting season -- occup dis due to absorp of nic)

GIGNOUX, M. et al (France), "Pronostic de tumeurs malignes du bord de langue," J Fr Otorhinolaryngol 21/1: 25-6, Jan 1972. (Rev of malig of tongue; 95% of pts smoked & drank alcohol)

GODIN, G. et al (Toronto), "Urban exposure to carbon monoxide," Arch Environ Hlth 25/5: 305-13, Nov 1972. (Smkg can bring indoor conc above permitted 24-h levels)

GROVER, P.L. et al (England), "Formation of K-region epoxides as microsomal metabolites of pyrene and benzo[a]pyrene," Biochem Pharmac 21/20: 2713-26, October 15, 1972.

HALL, G.H. (England), "Changes in body temperature produced by cholinomimetic substances injected into cerebral ventricles of unanaesthetized cats," Br J Pharmac 44/4: 634-41, 1972. (Nic caused fall in body temp, skin vasodilat)

HERMANSEN, L. & KARLSEN, K. (Norway), "Maksimalt oksygenopptak hos unge Norske menn," T Norske Laegeforen 92/13: 929-36, May 10, 1972. (Tob smoking reduces level of physical performance; tob smoke contains 4% CO)

HOLDER, A.R. (Ill), "Law and Medicine: Lung Cancer," JAMA 222/7: 877-8, Nov 13, 1972. (Complainants rarely win malpractice suits against physicians when lung cancer is involved.)

KAUFMAN, D.G. et al (NCI), "Coordinated biochemical and morphologic examination of hamster tracheal epithelium," JNCI 49/3: 783-92, Sept 1972.

KLIMISCH, H.J. & STADLER, L. (W. Germany), "Gel-partition chromatographic processes for the preparative separation of polar substances from polycyclic aromatic hydrocartons. fractionation of cigarette smoke condensate," J Chromatogr 67/1: 175-8, 1972.

KOURI, R.E. et al (U. Tenn/Md), "Quantitation of aryl hydrocarbon hydroxylase activity in individual fetal hamster cells in vitro," JNCI 49/4: 993-1005, Oct 1972.

0023627071

Source: https://www.industrydocuments.ucsf.edu/docs/ptxk0000

KUPKE, I.R. (Cal), "Biosynthesis of lipids in perfused dog aorta and coronary artery. III. Incorporation of [2-^{14}C] acetate into sterols and uptake of [^{3}H]-cholesterol in three aortic layers and in coronary artery of normal and hyperlipemic dogs and under the influence of nicotine," J Mol Cell Cardiology 4: 255-68, 1972. (CTR-grant)

LANGE, I.R. et al (USSR), "Quantitative determination of nicotine by gas-liquid chromatography," Zdravookhranenie Kasakhsmaia 30/10: 26-8, 1971.

LEJEUNE, J. (France), "Essai d'analyse topologique du site cholinergique," C.R. Acad Sc Paris 274/26: 3630-1, June 26, 1972. (Disc of molecular surface features of cholinergic receptor sites, based on structure of nic, ACh & others)

LUBCHENCO, L.O. et al (Denver), "Neonatal mortality rate: Relationship to birth weight and gestational age," J of Pediatrics 81/4: 814-22, Oct 1972.

MILIEVSKAYA, I.L. & KISELEVA, N.S. (USSR), "On the effect of NAS on the liver in Syrian hamsters," Vop Onkol 18/3: 70-3, 1972.

RASMUSSEN, R.E. et al (U. of Cal), "Vitamin A-induced modification of benzo[a]pyrene metabolism in syrian hamster cell cultures," JNCI 49/3: 693-700, Sept 1972. (Treatmnt. of cells w vit A restored BP metabolizing act)

SAFFIOTTI, U. et al (NCI), "Respiratory tract carcinogenesis induced in hamsters by different dose levels of benzo[a]pyrene and ferric oxide," JNCI 49/4: 1199-1204, Oct 1972. (Pos correl betw dose level & yield of resp tumors)

SCHREIBER, H. et al (Oak Ridge, Tenn), "Induction of lung cancer in germfree, specific-pathogen-free, and infected rats by N-nitrosoheptamethyleneimine: Enhancement by respiratory infection," JNCI 49/4: 1107-14, Oct 1972.

THURN, G. (W Germany), "Nebenwirkungen verschiedener Medikamente am Auge," Forschr Med 90/16: 624-8, June 1, 1972. (Nic, as a ganglion blocking agent, is mentioned as a drug that causes glaucoma.)

VERDUN DI CANTOGNO, L. & DUGHERA, L. (Italy), "Importanza e distribuzione di alcune cause stressanti in 500 infarti del miocardio nella citta di Torino," Boll Soc Ital Cardiol 16/10: 609-10, 1971. (Smoking may be fact in MI when accompanied by hyperten)

WALLER, R.E. & BROOKS, A.G.F. (England), "Heights and weights of men visiting a public health exhibition," Brit J Prev Soc Med 26: 180-5, Aug 1972. (Diffs in wts for smkrs, non, and ex were small & non signif at all ages)

WITSCHI, H. & SAINT-FRANCOIS, B. (Montreal), "Enhanced activity of benzpyrene hydroxylase in rat liver and lung after acute Cannabis administration," Toxicol Appl Pharmacol 23/1: 165-8, September 1972.

0002367072

16. ERRATA

CD November 1972: - The senior author of the abstract on page 9 should read "OBERMAN, A." The author listed as "CHRISTOPHER, J." on page 34 should read "CASTON, J.C."

Source: https://www.industrydocuments.ucsf.edu/docs/ptxk0000